Evaluation the rule of NSAIDs in the creation and worsening of the upper gastrointestinal bleeding

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Abstract: Upper gastrointestinal bleeding (UGIB) is a life threatening problem worldwide. It is mentioned that using various drugs such as non steroidal anti inflammatory drugs (NSAIDs), antiplatelets and anticoagulants has higher bleeding risk in these patients. The aim of current study is to evaluate the role of NSAIDs, antiplatelets and anticoagulants in severity of UGIB. Eighty patients (52.5% male and 47.5% female with mean age of 52.90±20.35 years) with the history of NSAIDs use admitted with the diagnosis of UGIB in 2010 in gastroenterology Ward, Imam Reza hospital were studied. Patients' demographic findings, history of antiplatelets and anticoagulants use, endoscopic findings and patients' outcome were recorded. The most common referral cause was hematemesis (62.5%) and blood in gastric wash was observed in 22.5%. among patients, 67.5% used only one and 32.5% used multiple NSAIDs. Antiplatelets and anticoagulants were used along with NSAIDs in 35% and 30%, respectively. Ulcer was the commonest finding in endoscopy (77.5%). In 47.5% of cases, transfusion was needed and 17.5% had surgery. Hematemesis (p=0.003), hematochezia (p=0.03) and surgery (p=0.001) in patients with multiple NSAIDs use and blood and coffee-ground (p=0.001), unstable hemodynamic (p=0.02) and need for transfusion in patients with one NSAIDs use was significantly higher. Unstable hemodynamic was the only significantly difference between patients with use of only NSAIDs and NSAIDs and antiplatelets and/or anticoagulants (p=0.01). Patients with NSAIDs use would have severe symptoms if UGIB happens, especially in case of multiple NSAIDs use, there is the probability of uncontrollable bleeding and need for more aggressive treatments. Antiplatelets and anticoagulants use with NSAIDs increase the risk of severe clinical symptoms in UGIB.

[Eilyad Issabeagloo, Mahmoud tabatabaei, Mohammad Taghizadieh. **Evaluation the rule of NSAIDs in the creation and worsening of the upper gastrointestinal bleeding.** *Life Sci J* 2012;9(4):5091-5097] (ISSN:1097-8135). http://www.lifesciencesite.com. 759

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Keywords: Bleeding; Upper gastrointestinal tract; NSAIDs, antiplatelet agents, anticoagulation agent

1. Introduction

Upper gastrointestinal bleeding (UGIB) is an obvious and potential life threatening problem in all over the world. Despite advances in diagnosis and treatment, the mortality rate has remained steady (1). Upper gastrointestinal bleeding is about 4 times more common in comparison with bleeding in lower gastrointestinal. Upper gastrointestinal bleeding is one of the common disease and with the prevalence about 102 to 150 hospitalized person in year courses disability and heavy costs for treatment (2, 3).

Upper gastrointestinal bleeding may be due to different cases: Information from Saudi Arabia, Kuwait, Jordan, Greece and Iran, named two major causes of UGIB, peptic ulcer and esophageal varices. And use of NSAIDs and chronic infection with Helicobacter pylori were two major predisposing factors (4-8). Increasing life expectancy in developing countries leads to increased incidence of joint disorders which is along with increases in prescription of NSAID medicines (9). Although NSAIDs are effective, but using these medicines is along with several unpleasant reactions in different organs. Gastrointestinal complications are the most common type of these reactions and are along with dyspepsia, heartburn and gastric discomfort with the more severe events such as peptic ulcer with bleeding and perforation threatening complications (10, 11). Using these medicines increases the risk of bleeding and gastrointestinal complications compared to normal individuals (12, 13). It has been observed that using anti-coagulant and anti-platelet medicines was along with increases in the rate of UGIB. Gastrointestinal system is the most common place which patients have gastrointestinal bleeding because of taking edible anticoagulants (14). The number of UGIB patients who refer while taking warfarin, due to the increasing indications of anticoagulant medicines use, is increasing (15). Patients with artificial heart valves, attack or chronic atrial fibrillation, recurrent DVT, coagulation diseases and vascular diseases usually use anticoagulants for long term and they are at high risk of bleeding. Despite progresses in controlling gastrointestinal bleeding in these patients, extensive bleeding usually occurs in 20% of these patients (15-19). Considering contents, it is obvious that different factors put patients at the risk of gastrointestinal bleeding. This study is to evaluate the rule of anti-clotting, anti-platelet medicines and NSAIDs in causing and aggravation of upper gastrointestinal bleeding.

2. Materials and Methods

Study type is descriptive – sectional. In this of study, 80 patients diagnosed with upper gastrointestinal bleeding who were hospitalized in digestive section of Iran hospitals, were studied.

- *Inclusion criteria to study were as follows:*

1) Bleeding should only be of upper gastrointestinal.
2) Age should be over 14 years.
3) Patients with upper endoscopy and diagnosis of UGIB.
- *Exclusion criteria from the study were as follows:*
1) bleeding from the respiratory system (hemoptysis)
2) bleeding from the nasopharynx
3) lower gastrointestinal system's bleeding
4) gastrointestinal bleeding from unknown origin
5) upper gastrointestinal cancer
During the study, all patients' information, who were hospitalized with the diagnosis of upper gastrointestinal bleeding was evaluated using the clinical files of patients.
- *Variables which were studied are as follow:*
• Age, sex, main reason for referring, NGT status, Haemodynamic, The history of taking NSAID, anticoagulants or antiplatelets, Endoscopy diagnosis, The rate of blood transfusion, Duration of hospitalization, Type of operation, the existence or non-occurrence of death
- *Ethical considerations:*
All patients' information were obtained from clinical files. All patients' information was strictly confidential and we will not mention about it anywhere. All diagnostic and therapeutic procedures were in the course of the disease and no additional costs were imposed to the patients.

3. Statistical analysis
All data were analyzed using statistical software SPSS16. Descriptive statistics methods (frequencies, percentages) were used for statistical evaluation. For comparing qualitative results the statistical test (Chi Square) was used. Less than 0.05 P value was considered significant in this study.

4. Results
200 patients with upper gastrointestinal bleeding with a history of using NSAIDs we examined.

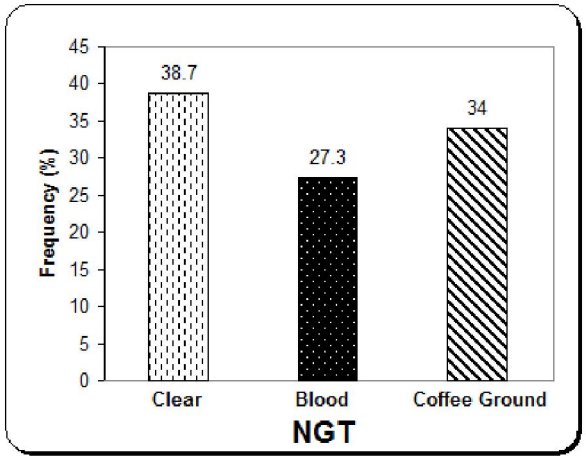

Figure 1. Status of NGT in patients. Results expressed as Frequency.

- *Demographic findings:*
Mean age of patients was 44.67 ± 13.21 years old with a median of 45 years. It is observed that most male patients with UGIB are slightly larger.
- *Reason for referring:*
In 125 cases (62.5%) Hematemesis, in 70 cases (35%) Melena, and in 60 cases (30%) was Hematochezia. In some cases, patients simultaneously had two complaints.
- *Status of NGT:*
Figure 1 shows NGT Status of the patients. As it can be seen, clear blood was founded only in 38.7 % of patients. Blood is mostly clear or sufficient ground.
- *Haemodynamic status:*
Figure 2 shows the haemodynamic status of patients. As it can be seen half of the patients had haemodynamic instability that in two cases (3.2%) patients were in shock.

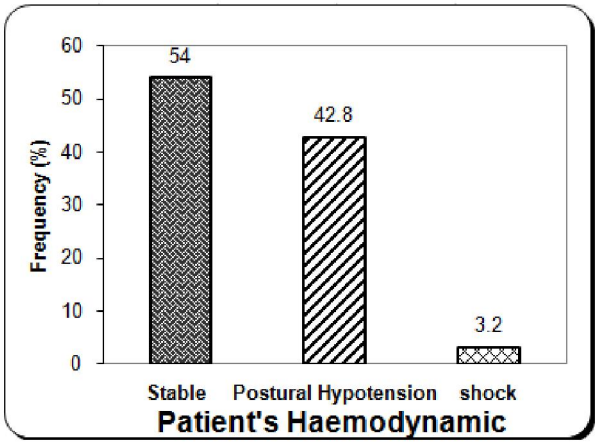

Figure 2. haemodynamic status of patients. Results expressed as Frequency.

As seen in the figure, Most patients at the time of entry into the department in terms of hemodynamic were stable or had conditional hypotension.
- *Medical history:*
In 135 cases (67.5%) patients were using on NSAIDs medicines and in 65 cases (32.5%) patients were using two or more NSAIDs medicines. Anti-platelet medicines in 70 cases (35%) and anticoagulation medicines in 60 cases (30%) of patients were simultaneously taking with NSAIDs.
- *Endoscopic findings:*
In 165 cases (82/5%) of patients Ulcer was identified that in 65 cases (32.5%) it was gastric ulcer, in 40 cases (20%) it was duodenal ulcer and in 50 cases (25%) it was esophageal oesophagitis = erosions.
In 45 cases (22.5%) erosive lesions in the stomach (gastritis erosive) existed. In 40 cases (20%) other findings were led to bleeding. Also in 20 cases (10%) it was esophageal varices and in 5 cases (2.5%) it was Mallory–Weiss. Different findings were observed simultaneously in some patients.
- *Blood transfusion:*

In 95 cases (47.5%) blood transfusions was required.

Mean received blood levels was 3.22 ± 0.31 units with the median of 2 units. The lowest and highest received blood were respectively 1 and 9 units. In 20 cases (10%), FFP was received that the average receive of FFP was 4.82 ± 3.65 units with the median of 2 units.

- *Average duration of hospitalization:*

Average duration of hospitalization was 7 ±3.34 with the median of 5 days. Minimum and maximum duration of hospitalization was respectively 2 and 15 days.

- *Surgery:*

In 35 cases (17.5%) of patients surgery was required because there was extensive bleeding.

- *Mortality:*

In this study 6 cases (3%), mortality was observed. Different findings among the consumption of one or more NSAIDs were compared.

Figure 3 shows the frequency of Hematemesis among two groups. As it can be seen in patients who were taking a few NSAIDs simultaneously, Hematemesis rate is markedly higher (p=0.003). Melena was in 55 cases (27.5%) who were taking one NSAIDs and 23 cases (11.5%) who were taking several types of NSAIDs. The difference between two groups was not statistically significant (p=0.23). Hematochezia was also seen in 27 cases (13.5%) of patients who were taking one type of NSAIDs and in 36 cases (18%) of patients who were taking several types of NSAIDs. Hematochezia is markedly more in patients who are taking several types of NSAIDs. (p=0.037).

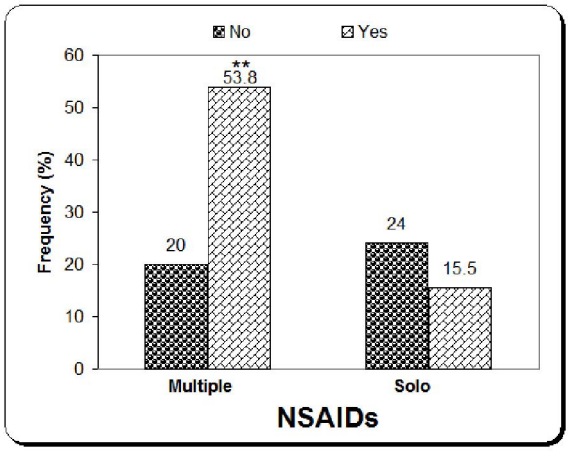

Figure 3. Frequency of Hematemesis among two groups. Hematemesis statistics is greater in the patients who are taking more than one type of NSAIDs. Results expressed as Frequency. **p<0.01

Figure 4 shows the results of NGT in two groups. As it can be seen clear and Grande adequate bleeding in NSAIDs user cases is more (p=0.001). From the standpoint of Haemodynamic in groups who were using one or several types of NSAIDs, stable condition , respectively was found in 35 cases (38.4%) and 16 cases (61.5%), orthostatic hypotension respectively was found in 75 cases (55.6%) and 20 cases (30.8%) and shock was found in 5 cases (14.3%). There were significant differences between two groups (p=0.02). In the group who were taking one type of NSAIDs, peptic ulcer in 14 cases (29.2%) and duodenum in 35 cases (29.2%) and esophageal erosions in 50 cases (41.7%) was found. What were mentioned above, in the group who were taking several types of NSAIDs, were respectively 30 cases (85.7%), 5 cases (14/3%) and 0. It is observed, in patients who were taking several types of NSAIDs, gastric ulcer was markedly more common (p=0/001). Erosive lesions was in 20 cases (14.8%) of patients who were taking one type of NSAIDs and 25 cases (38.5%) of patients who were taking several type of NSAIDs. The difference between two groups was not significant in this case (p=0.027).

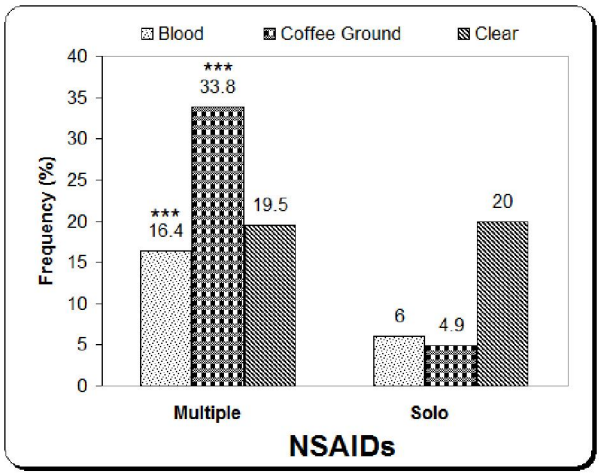

Figure 4. Results of NGT in two groups. Results expressed as Frequency. ***p<0.001.

Figure 5 shows the need for blood in two groups of patients who were taking one or several type of NSAIDs. Significantly, Patients who were taking on type of NSAIDs need to receive more blood. (p=0.005). Require for Transfusion is more in patients who were taking several types of NSAIDs.

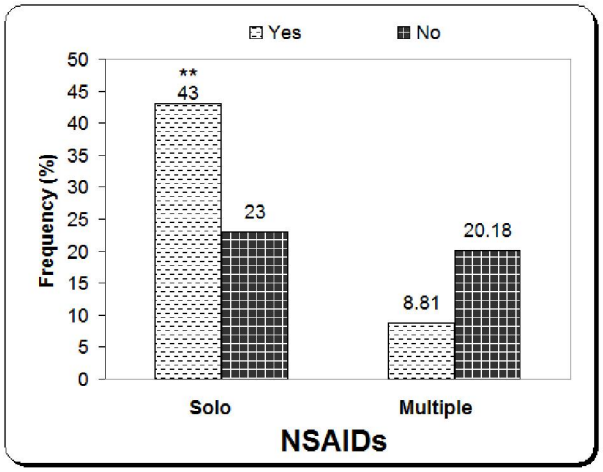

Figure 5. The need for blood Transfusion in two groups of patients who were taking one or several type of NSAIDs. Results expressed as Frequency. **p<0.01

Figure 6 shows the rate of need for surgery in patients who were taking one or several types of NSAIDs.

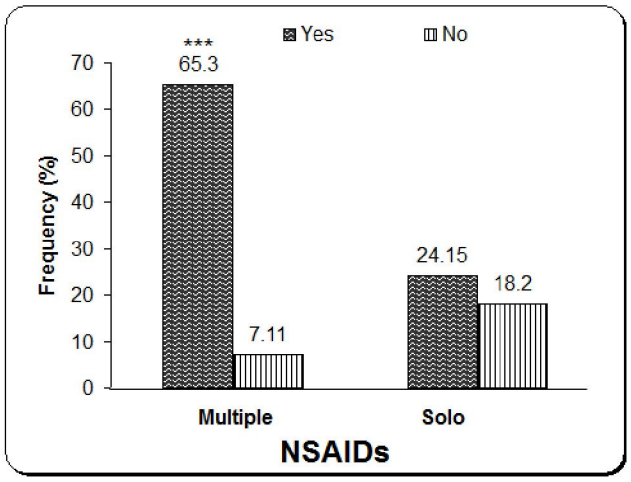

Figure 6. Rate of need for surgery in patients who were taking one or several types of NSAIDs

As it can be seen in the diagram, the need for surgery in patients who were taking several type of NSAIDs, was significantly more because of the lack of bleeding control and patients inadequate haemodynamic status (p=0.002). Hospitalization duration, for patients who were taking one type of NSAIDs was 5.23±2.89 and for patients who were taking several types of NSAIDs was 6.21±4.19. It can be seen that patients who were taking several types of NSAIDs had longer hospital stay due to the severity of symptoms, however the difference between two groups is not statistically significant (p=0.22).

In 110 cases (55%), patients were taking only NSAIDs medicine category (first group) and in 90 cases (45%) patients were taking NSAIDs with anticoagulants or anti-platelet medicines (second group). Results between these two groups were also compared. 50 cases (55.6%) of patients in first group and 75 cases (68.2%) of patients in second group had Hematemesis. There was no significant difference between the two groups in this case. (p=0.34). Need for surgery in patients who were taking several types of NSAIDs is more. Melena in first and second group respectively was in 35 cases (38.9%) and 35 cases (31.8%) patients. There was no significant difference between the two groups (p=0.65). Hematochezia in first and second group respectively was in 35 cases (38.9%) and 25 cases (22.7%). In this case also, there was no significant difference between the two groups (p=0.27).

In NGT findings, in the first group, bright blood was in 9 cases (11.7%), coffee ground was in 23 cases (42.4%), and clear blood without any specific findings was in 37 cases (39.1%) of patients. What were mentioned above, in the second group were respectively, 30 cases (27.3%), 35 cases (31.8%) and 45 cases (40.9%). It can be seen that active bleeding in patients who take several medicines is more, however there is no significant difference in this case (p=0.39). Stable haemodynamic status in first and second group was respectively in 30 cases (33.3%) and 70 cases (63.6%) of patients, orthostatic hypotension, was respectively in 55 cases (61.1%) and 45 cases (36.4%) of patients and shock respectively was in 5 cases (5.6%) and 0 cases. Markedly, the rate of unstable haemodynamic was higher in the cases who used only NSAIDs (p=0.01).

The need for blood transfusions in first group was in 40 cases (44.4%) and in second group was in 55 cases (50%) of patients. It can be seen that the rate of need for blood transfusions in the group who is treated with several groups of medicines is higher. However, the difference between groups was not significant (p=0.65). Surgery was needed in the first and second group respectively in 10 cases (11.1%) and 25 cases (22.7%) of patients. It can be seen that in this case, the need of surgery, for the group who is treated whit several groups of medicines is more. Although this difference was not statistically significant (p=0.24). The mean hospital stay in first group was 6.41 ±1.72 and in the second group was 4.11 ±1.29.

The difference between the two groups was not statistically significant (p=0.43). Between patients with and without anti-platelet consumption, need for blood respectively was in 14 cases (50%) and 24 cases (46.2%). There was no significant difference in this case (p=0.54). Surgery in cases with and without anti-platelet consumption respectively was needed in 20 cases (28.6%) and 15 cases (11.5%). There was also no significant difference in this case (p=0.06). The need for blood products in patients who with and without anticoagulation consumption respectively was found in 35 (58.3%) and 60 (42.9%) cases of patients. There was no statistically significant difference between the two groups (p=0.41). The need for surgery in patients who with and without anticoagulation consumption respectively was found in 5 (8.3%) and 30 (21.4%) cases of patients. There was no statistically significant difference between the two groups (p=0.2). Due to low mortality (10 cases, 10%) evaluating the rule of NSAIDs, statistically was not possible. It is hoped in future joint this issue should be discussed.

5. Discussion

Upper gastrointestinal bleeding (UGIB) is an obvious potentially life threatening problem all over the world. Despite advances in diagnosis and treatment, the mortality rate has remained steady (1). Anticoagulation treatment creates problems in managing the gastrointestinal bleeding. The most important site with obvious bleeding in patients who received edible anticoagulation therapy is the gastrointestinal system (14). One-fourth to one –third population over 65 years, use anticoagulant medicines. In clinical trials these medicines were along with increased risk of UGIB. It is surprising that, very little is known about the epidemiology poisoning effect of these medicines and bleeding. Except for low dose aspirin, there is very rare information about risks along with non salicylates medicines and its interaction with other danger factors. In contrast, prevention of UGIB in patients who use anti-

platelet medicines is only evaluated for high risk patients, like patients who have a history of UGIB (29, 30). While the information is not available in other groups which are at risk. It has been clearly shown that Aspirin and NSAIDs increase the risk of upper gastrointestinal bleeding (20). In fact, because the upper gastrointestinal bleeding is common, it seems that it's the most important and serious complication, about using this class of medicines (21). Use of these medicines increases the bleeding risk and gastrointestinal complication, 3 to 5 time more than common individuals (12, 13). Anti platelet therapy is effective in reducing the incidence of cerebral vascular accidents, myocardial infarction and death because of cardiovascular reasons in patients with symptomatic Atrothrombotic diseases (31). As described previously, the simultaneous use of NSAIDs and anticoagulation medicines is along with increases risk of UGIB (32). In patients treated with anti platelet, use of NSAIDs should be avoided when it is possible. In few patients who really need to use these group of medicines, concurrent use of PPl can reduce the risk of UGIB. In the current study we investigated the upper gastrointestinal bleeding cases, in patients with the history of taking NSAIDs. It was observed that major bleeding was accrued in the consumption of one type of NSAIDs. And in cases which used one type of unstable haemodynamic NSAIDs, need for blood transfusion was more. However the lack of proper endoscopic control and surgery was more while using several types of NSAIDs. In this study, patients were 58.7% male, 41.3% female with the mean age 44.67 ±13.21 years old. In Marco and his colleagues study male to female ratio also was higher and the mean age was 71.5 ± 13.8 years old (28). In the present study, the most common reason to refer was Hematemesis and bright blood was observed in 27.3% cases of stomach washing. The most common findings were about ulcer endoscopic (77.5%), particularly peptic ulcer. In 47.5 % of patients blood transfusions was required and 17.5% had surgery. In Elghuel's study also peptic ulcer (37.1%) was the most common causes of UGIB (26), however, unlike the present study; duodenal ulcer was the most common type. Several factors increase the risk of gastrointestinal complications of using NSAIDs such as aspirin. These factors include the history of gastric ulcer or Gastrointestinal complications, older age, congestive heart disease and the treatment simultaneously with anticoagulants or corticosteroids (22, 23). Among these factors, the history of gastrointestinal bleeding with high risk for recurrent bleeding is there for NSAIDs users (22, 24). Concurrent use of NSAIDs and anticoagulant medicines was along with increased risk of UGIB (32). Ibanez and colleagues estimated the risk of UGIB which is related to anti-platelet medicines and the risk score for UGIB occurrence for Aspirin was 4, for Clopidogrel was 2.3, for Amvl Dypyryd was 0.9, for Ticlopidine was 3.1 and for Flvsal was 1.6. Concurrent use of proton pump inhibitors reduced all of the risks. Anti-platelet medicines were responsible for 14.5% of UGIBs (33).García Rodríguez and Jick also observed during one study that the risk of bleeding in patients treated with NSAIDs, who concurrently used anticoagulants or corticosteroids, is more (25). In Thomopoulos and colleagues study, major of patients who used NSAIDs and anticoagulants simultaneously (74.3%), had peptic ulcer as the cause of bleeding (38). In the present study anti-platelet medicines in 35% and anticoagulant medicines in 30% were used simultaneously with NSAIDs. In Marco and his colleagues' study, of the causes of bleeding in patients treated with NSAIDs in 16.7%, it was because of using other medicines simultaneously (28). But in Laszlo and colleagues study there was no difference between users and non users in the clinical presentation, location of bleeding or frequency of symptoms. 40% in each group did not have any symptoms before the onset of bleeding. Blood receive rate in patients who received NSAIDs was slightly higher. There was no difference in terms of frequency of surgical intervention (27). In this study, also the only significant difference between two groups was in taking NSAIDs alone or in combination with anticoagulants and / or unstable homodynamic anti-platelet which was more in first group. However, in present study, despite observed aggravation of bleeding and its complications, there was no significant statistically difference between anticoagulant consumers and non consumers and anti-platelet consumers and non consumers in term of need for blood and surgery. (Probably it was due to low number of patients or because medical center is referral). In the present study it was observed that Hematemesis, Hematochezia and surgery were markedly more in patients who used several types of NSAIDs and bright bleeding, coffee ground, unstable homodynamic and need for blood were markedly more in patients who used one type of NSAIDs.

6. Conclusion

Patients who took NSAIDs had more severe symptoms of bleeding and particularly in patients who took several types of NSAIDs simultaneously, the possibility of uncontrollable bleeding and need for more invasive treatment measures were more. Using Anti-platelet and anticoagulation simultaneously with NSAIDs did not increase the risk of severe symptoms.

7. Suggestions

The results of this study demonstrated that, patients who are taking NSAIDs are in a high risk of complications and problems of gastrointestinal bleeding. Particularly in cases who are taking several types of NSAIDs simultaneously. It is recommended to inhibit patients, taking NSAIDs medicines as possible, particularly several types of NSAIDs simultaneously and it should be prescribed only for cases with indication. It was also observed that patients who were taking Anti-platelet and/or anticoagulation had some difference with patients who didn't take it but the difference was not statistically significant. However to confirm the findings, it is recommended to do another study with larger sample size and considering the control group included patients with

UGIB, without taking NSAIDs and anti-platelet and anticoagulant for better and more accurate results.

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10/4/2012